Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Laboratory Testing

Laboratory Testing for Initial Assessment and Monitoring While on Antiretroviral Therapy (Last updated February 12, 2013; last reviewed February 12, 2013)

A number of laboratory tests are important for initial evaluation of HIV-infected patients upon entry into care, during follow-up (if antiretroviral therapy (ART) has not been initiated), and before and after the initiation or modification of therapy to assess virologic and immunologic efficacy of ART and to monitor for laboratory abnormalities that may be associated with antiretroviral (ARV) drugs. Table 3 outlines the Panel's recommendations for the frequency of testing. As noted in the table, some tests may be repeated more frequently if clinically indicated.

Two surrogate markers are routinely used to assess the immune function and level of HIV viremia: CD4 T-cell count (CD4 count) and plasma HIV RNA (viral load). Resistance testing should be used to guide selection of an ARV regimen; a viral tropism assay should be performed before initiation of a CCR5 antagonist; and HLA-B*5701 testing should be performed before initiation of abacavir (ABC). The rationale for and utility of these laboratory tests are discussed below.

Table 3. Laboratory Monitoring Schedule for Patients Before and After Initiation of Antiretroviral Therapy[a] (page 1 of 2)

	Entry into care	Follow-up before ART	ART initiation or modification[b]	Follow-up 2–8 weeks post-ART initiation or modification	Every 3–6 months	Every 6 months	Every 12 months	Treatment failure	Clinically indicated
HIV serology	√ If diagnosis has not been confirmed								
CD4 count	√	√ Every 3–6 months	√		√	In clinically stable patients with suppressed viral load, CD4 count can be monitored every 6–12 months (see text).		√	√
HIV viral load	√	√ Every 3–6 months	√	√[c]	√[d]			√	√
Resistance testing	√		√[e]					√	√
HLA-B*5701 testing			√ If considering ABC						
Tropism testing			√ If considering a CCR5 antagonist					√ If considering a CCR5 antagonist, or for failure of CCR5 antagonist-based regimen	√
Hepatitis B serology[f]	√		√ May repeat if HBsAg (-) and HBsAb (-) at baseline						√
Hepatitis C serology, with confirmation of positive results	√								√
Basic chemistry[g,h]	√	√ Every 6–12 months	√	√	√				√

Table 3. Laboratory Monitoring Schedule for Patients Before and After Initiation of Antiretroviral Therapy[a] (page 2 of 2)

	Entry into care	Follow-up before ART	ART initiation or modification[b]	Follow-up 2–8 weeks post-ART initiation or modification	Every 3–6 months	Every 6 months	Every 12 months	Treatment failure	Clinically indicated
ALT, AST, T. bilirubin	√	√ Every 6–12 months	√	√	√				√
CBC with differential	√	√ Every 3–6 months	√	√ If on ZDV	√				√
Fasting lipid profile	√	√ If normal, annually	√	√ Consider 4–8 weeks after starting new ART regimen that affects lipids		√ If abnormal at last measurement	√ If normal at last measurement		√
Fasting glucose or hemoglobin A1C	√	√ If normal, annually	√		√ If abnormal at last measurement	√ If normal at last measurement			√
Urinalysis[g]	√		√			√ If on TDF[i]	√		√
Pregnancy test			√ If starting EFV						√

[a] This table pertains to laboratory tests done to select an ARV regimen and monitor for treatment responses or ART toxicities. Please refer to the HIV Primary Care guidelines for guidance on other laboratory tests generally recommended for primary health care maintenance of HIV patients.[1]

[b] ART may be modified for treatment failure, adverse effects, or regimen simplification.

[c] If HIV RNA is detectable at 2 to 8 weeks, repeat every 4 to 8 weeks until suppression to <200 copies/mL, then every 3 to 6 months.

[d] Viral load typically is measured every 3 to 4 months in patients on ART. However, for adherent patients with suppressed viral load and stable immunologic status for more than 2 to 3 years, monitoring at 6 month intervals may be considered.

[e] In ART-naive patients, if resistance testing was performed at entry into care, repeat testing before initiation of ART is optional. The exception is pregnant women; repeat testing is recommended in this case. For virologically suppressed patients who are switching therapy for toxicity or convenience, viral amplification will not be possible and therefore resistance testing should not be performed. Results from prior resistance testing can be used to help in the construction of a new regimen.

[f] If HBsAg is positive at baseline or before initiation of ART, TDF plus either FTC or 3TC should be used as part of the ARV regimen to treat both HBV and HIV infections. If HBsAg, and HBsAb, and anti-HBc are negative at baseline, hepatitis B vaccine series should be administered.

[g] Serum Na, K, HCO_3, Cl, BUN, creatinine, glucose (preferably fasting). Some experts suggest monitoring the phosphorus levels of patients on TDF. Determination of renal function should include estimation of CrCl using Cockcroft-Gault equation or estimation of glomerular filtration rate based on MDRD equation.

[h] For patients with renal disease, consult the Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America.[2]

[i] More frequent monitoring may be indicated for patients with evidence of kidney disease (e.g. proteinuria, decreased glomerular dysfunction) or increased risk of renal insufficiency (e.g., patients with diabetes, hypertension).

Acronyms: 3TC = lamivudine, ABC = abacavir, ALT = alanine aminotransferase, ART = antiretroviral therapy, AST = aspartate aminotranserase, CBC = complete blood count, CrCl = creatinine clearance, EFV = efavirenz, FTC = emtricitabine, HBsAb = hepatitis B surface antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, MDRD = modification of diet in renal disease (equation), TDF = tenofovir, ZDV = zidovudine

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CD4 T-Cell Count (Last updated February 12, 2013; last reviewed February 12, 2013)

The CD4 T-cell count (CD4 count) serves as the major laboratory indicator of immune function in patients who have HIV infection. It is one of the key factors in determining both the urgency of antiretroviral therapy (ART) initiation and the need for prophylaxis for opportunistic infections. It is also the strongest predictor of subsequent disease progression and survival according to findings from clinical trials and cohort studies.[1, 2] CD4 counts are highly variable; a significant change (2 standard deviations) between 2 tests is approximately a 30% change in the absolute count, or an increase or decrease in CD4 percentage by 3 percentage points.

- **Use of CD4 Count for Initial Assessment.** The CD4 count is one of the most important factors in determining the urgency of ART initiation and the need for prophylaxis for opportunistic infections. All patients at entry into care should have a baseline CD4 count **(AI)**. Recommendations for initiation of ART can be found in the Initiating Antiretroviral Therapy in Antiretroviral-Naive Patients section of these guidelines.
- **Use of CD4 Count for Monitoring Therapeutic Response.** An adequate CD4 response for most patients on therapy is defined as an increase in CD4 count in the range of 50 to 150 cells/mm^3 per year, generally with an accelerated response in the first 3 months of treatment. Subsequent increases in patients with good virologic control average approximately 50 to 100 cells/mm^3 per year until a steady state level is reached.[3] Patients who initiate therapy with a low CD4 count[4] or at an older age[5] may have a blunted increase in their counts despite virologic suppression.

Frequency of CD4 Count Monitoring. ART now is recommended for all HIV-infected patients. In untreated patients, CD4 counts should be monitored every 3 to 6 months to determine the urgency of ART initiation. In patients on ART, the CD4 count is used to assess the immunologic response to ART and the need for initiation or discontinuation of prophylaxis for opportunistic infections **(AI)**.

The CD4 count response to ART varies widely, but a poor CD4 response is rarely an indication for modifying a virologically suppressive antiretroviral (ARV) regimen. In patients with consistently suppressed viral loads who have already experienced ART-related immune reconstitution, the CD4 cell count provides limited information, and frequent testing may cause unnecessary anxiety in patients with clinically inconsequential fluctuations. Thus, for the patient on a suppressive regimen whose CD4 cell count has increased well above the threshold for opportunistic infection risk, the CD4 count can be measured less frequently than the viral load. In such patients, CD4 count may be monitored every 6 to 12 months, unless there are changes in the patient's clinical status, such as new HIV-associated clinical symptoms or initiation of treatment with interferon, corticosteroids, or anti-neoplastic agents **(CIII)**.

Factors that affect absolute CD4 count. The absolute CD4 count is a calculated value based on the total white blood cell (WBC) count and the percentages of total and CD4+ T lymphocytes. This absolute number may fluctuate in individuals or may be influenced by factors that may affect the total WBC count and lymphocyte percentages, such as use of bone marrow-suppressive medications or the presence of acute infections. Splenectomy[6, 7] or co-infection with human T-lymphotropic virus type I (HTLV-1)[8] may cause misleadingly elevated absolute CD4 counts. Alpha-interferon, on the other hand, may reduce the absolute CD4 count without changing the CD4 percentage.[9] In all these cases, CD4 percentage remains stable and may be a more appropriate parameter to assess the patient's immune function.

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Plasma HIV-1 RNA Testing (Last updated February 12, 2013; last reviewed February 12, 2013)

Plasma HIV-1 RNA (viral load) should be measured in all HIV-1-infected patients at baseline and on a regular basis thereafter, especially in patients who are on treatment, because viral load is the most important indicator of response to antiretroviral therapy (ART) **(AI)**. Commercially available HIV-1 RNA assays do not detect HIV-2 viral load. For further discussion on HIV-2 RNA monitoring in patients with HIV-1/HIV-2 co-infection or HIV-2 mono-infection, see HIV-2 Infection. Analysis of 18 trials that included more than 5,000 participants with viral load monitoring showed a significant association between a decrease in plasma viremia and improved clinical outcome.[1] Thus, viral load testing serves as a surrogate marker for treatment response[2] and can be useful in predicting clinical progression.[3, 4] The minimal change in viral load considered to be statistically significant (2 standard deviations) is a threefold, or a 0.5 $\log_{10}$ copies/mL change.

Optimal viral suppression is generally defined as a viral load persistently below the level of detection (<20 to 75 copies/mL, depending on the assay used). However, isolated blips (viral loads transiently detectable at low levels, typically <400 copies/mL) are not uncommon in successfully treated patients and are not thought to represent viral replication or to predict virologic failure.[5] In addition, low-level positive viral load results (typically <200 copies/mL) appear to be more common with some viral load assays than with others. Furthermore, there is no definitive evidence that patients with viral loads quantified as <200 copies/mL using these assays are at increased risk for virologic failure.[6-8] For the purposes of clinical trials, the AIDS Clinical Trials Group (ACTG) currently defines virologic failure as a confirmed viral load >200 copies/mL, which eliminates most cases of apparent viremia caused by blips or assay variability.[9] This definition also may be useful in clinical practice (see Virologic and Immunologic Failure).

For most individuals who are adherent to their antiretroviral (ARV) regimens and who do not harbor resistance mutations to the prescribed drugs, viral suppression is generally achieved in 12 to 24 weeks, although it may take longer in some patients. Recommendations for the frequency of viral load monitoring are summarized below.

- **At initiation or change in therapy.** Plasma viral load should be measured before initiation of therapy and preferably within 2 to 4 weeks, and not more than 8 weeks, after treatment initiation or after treatment modification **(BI)**. Repeat viral load measurement should be performed at 4- to 8-week intervals until the level falls below the assay's limit of detection **(BIII)**.
- **In virologically suppressed patients in whom therapy was modified because of drug toxicity or for regimen simplification.** Viral load measurement should be performed within 2 to 8 weeks after changing therapy. The purpose of viral load monitoring at this point is to confirm potency of the new regimen **(BIII)**.
- **In patients on a stable ARV regimen.** Viral load should be repeated every 3 to 4 months or as clinically indicated **(BII)**. Clinicians may extend the interval to every 6 months for adherent patients who have suppressed viral loads for more than 2 to 3 years and whose clinical and immunologic status is stable **(BIII)**.

Monitoring in patients with suboptimal response. In addition to viral load monitoring, a number of additional factors should be assessed, such as adherence to prescribed medications, altered pharmacology, or drug interactions. Patients who fail to achieve viral suppression should undergo resistance testing to aid in the selection of an alternative regimen, as discussed in Drug-Resistance Testing and Virologic and Immunologic Failure **(AI)**.

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Drug-Resistance Testing (Last updated February 12, 2013; last reviewed February 12, 2013)

Panel's Recommendations
• HIV drug-resistance testing is recommended in persons with HIV infection at entry into care regardless of whether antiretroviral therapy (ART) will be initiated immediately or deferred **(AII)**. If therapy is deferred, repeat testing should be considered at the time of ART initiation **(CIII)**. • Genotypic testing is recommended as the preferred resistance testing to guide therapy in antiretroviral (ARV)-naive patients **(AIII)**. • Standard genotypic drug-resistance testing in ARV-naive persons involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers may wish to supplement standard genotypic resistance testing with an INSTI genotype test **(CIII)**. • HIV drug-resistance testing should be performed to assist in the selection of active drugs when changing ARV regimens in persons with virologic failure and HIV RNA levels >1,000 copies/mL **(AI)**. In persons with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**. • Drug-resistance testing should also be performed when managing suboptimal viral load reduction **(AII)**. • In persons failing INSTI-based regimens, genotypic testing for INSTI resistance should be performed to determine whether to include a drug from this class in subsequent regimens **(AII)**. • Drug-resistance testing in the setting of virologic failure should be performed while the person is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy **(AII)**. • Genotypic testing is recommended as the preferred resistance testing to guide therapy in patients with suboptimal virologic responses or virologic failure while on first or second regimens **(AII)**. • The addition of phenotypic to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns, particularly to protease inhibitors (PIs) **(BIII)**. • Genotypic resistance testing is recommended for all pregnant women before initiation of ART **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)** (see the *Perinatal Treatment Guidelines* for more detailed discussion). ***Rating of Recommendations:*** *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Genotypic and Phenotypic Resistance Assays

Genotypic and phenotypic resistance assays are used to assess viral strains and inform selection of treatment strategies. Standard assays provide information on resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Testing for integrase and fusion inhibitor resistance can also be ordered separately from several commercial laboratories. Co-receptor tropism assays should be performed whenever the use of a CCR5 antagonist is being considered. Phenotypic co-receptor tropism assays have been used in clinical practice. A genotypic assay to predict co-receptor use is now commercially available (see Co-receptor Tropism Assays).

Genotypic Assays

Genotypic assays detect drug-resistance mutations present in relevant viral genes. Most genotypic assays involve sequencing of the RT and PR genes to detect mutations that are known to confer drug resistance. Genotypic assays that assess mutations in the integrase and gp41 (envelope) genes are also commercially available. Genotypic assays can be performed rapidly and results are available within 1 to 2 weeks of sample collection. Interpretation of test results requires knowledge of the mutations selected by different antiretroviral (ARV) drugs and of the potential for cross resistance to other drugs conferred by certain mutations. The International AIDS Society-USA (IAS-USA) maintains an updated list of significant resistance-associated mutations in the RT, PR, integrase, and envelope genes (see

http://www.iasusa.org/resistance_mutations).[1] The Stanford University HIV Drug Resistance Database (http://hivdb.stanford.edu) also provides helpful guidance for interpreting genotypic resistance test results. Various tools to assist the provider in interpreting genotypic test results are now available.[2-5] Clinical trials have demonstrated that consultation with specialists in HIV drug resistance improves virologic outcomes.[6] Clinicians are thus encouraged to consult a specialist to facilitate interpretation of genotypic test results and design of an optimal new regimen.

Phenotypic Assays

Phenotypic assays measure the ability of a virus to grow in different concentrations of ARV drugs. RT and PR gene sequences and, more recently, integrase and envelope sequences derived from patient plasma HIV RNA are inserted into the backbone of a laboratory clone of HIV or used to generate pseudotyped viruses that express the patient-derived HIV genes of interest. Replication of these viruses at different drug concentrations is monitored by expression of a reporter gene and is compared with replication of a reference HIV strain. The drug concentration that inhibits viral replication by 50% (i.e., the median inhibitory concentration [IC_{50}]) is calculated, and the ratio of the IC_{50} of test and reference viruses is reported as the fold increase in IC_{50} (i.e., fold resistance).

Automated phenotypic assays that can produce results in 2 to 3 weeks are commercially available, but they cost more to perform than genotypic assays. In addition, interpretation of phenotypic assay results is complicated by incomplete information regarding the specific resistance level (i.e., fold increase in IC_{50}) that is associated with drug failure, although clinically significant fold increase cutoffs are now available for some drugs.[7-11] Again, consultation with a specialist to interpret test results can be helpful.

Further limitations of both genotypic and phenotypic assays include lack of uniform quality assurance testing for all available assays, relatively high cost, and insensitivity to minor viral species. Despite being present, drug-resistant viruses that constitute less than 10% to 20% of the circulating virus population will probably not be detected by commercially available assays. This limitation is important because after drugs exerting selective pressure on drug-resistant populations are discontinued, a wild-type virus often re-emerges as the predominant population in the plasma. As a consequence, the proportion of virus with resistance mutations decreases to below the 10% to 20% threshold.[12-14] In the case of some drugs, this reversion to predominantly wild-type virus can occur in the first 4 to 6 weeks after the drugs are discontinued. Prospective clinical studies have shown that despite this plasma reversion, re-initiation of the same ARV agents (or those sharing similar resistance pathways) is usually associated with early drug failure, and that the virus present at failure is derived from previously archived resistant virus.[15] Therefore, resistance testing is of greatest value when performed before or within 4 weeks after drugs are discontinued **(AII)**. Because resistant virus may persist in the plasma of some patients for longer periods of time, resistance testing done 4 to 6 weeks after discontinuation of drugs may still detect mutations. However, the absence of detectable resistance in such patients must be interpreted with caution when designing subsequent ARV regimens.

Use of Resistance Assays in Clinical Practice (See Table 4)

Use of Resistance Assays in Determining Initial Treatment

Transmission of drug-resistant HIV strains is well documented and associated with suboptimal virologic response to initial antiretroviral therapy (ART).[16-19] The likelihood that a patient will acquire drug-resistant virus is related to the prevalence of drug resistance in HIV-infected persons engaging in high-risk behaviors in the community. In the United States and Europe, recent studies suggest that the risk that transmitted virus will be resistant to at least one ARV drug is in the range of 6% to 16%.[20-25] Up to 8%, but generally less than 5% of transmitted viruses will exhibit resistance to drugs from more than one class.[24, 26-28]

If the decision is made to initiate therapy in a person with early HIV infection, resistance testing at baseline

can guide regimen selection to optimize virologic response. Therefore, resistance testing in this situation is recommended **(AII)**. A genotypic assay is preferred for this purpose **(AIII)**. In this setting, treatment initiation should not be delayed pending resistance testing results. Once results are obtained, the treatment regimen can be modified if warranted (see Acute and Recent HIV Infection). In the absence of therapy, resistant viruses may decline over time to less than the detection limit of standard resistance tests, but when therapy is eventually initiated, resistant viruses even at a low level may still increase the risk of treatment failure.[29-31] Therefore, if therapy is deferred, resistance testing should still be done during acute HIV infection **(AIII)**. In this situation, the genotypic resistance test result may be kept on record until the patient is to be started on ART. Repeat resistance testing at the time treatment is started should be considered because it is possible for a patient to acquire drug-resistant virus (i.e., superinfection) between entry into care and initiation of ART **(CIII)**.

Performing drug-resistance testing before ART initiation in patients with chronic HIV infection is less straightforward. The rate at which transmitted resistance-associated mutations revert to wild-type virus has not been completely delineated, but mutations present at the time of HIV transmission are more stable than those selected under drug pressure. It is often possible to detect resistance-associated mutations in viruses that were transmitted several years earlier.[32-34] No prospective trial has addressed whether drug-resistance testing before initiation of therapy confers benefit in this population. However, data from several, but not all, studies suggest that virologic responses in persons with baseline resistance mutations are suboptimal.[16-19, 35-37] In addition, a cost-effectiveness analysis of early genotypic resistance testing suggests that baseline testing in this population should be performed.[38] Therefore, resistance testing in chronically infected persons is recommended at the time of entry into HIV care **(AII)**. Although no definitive prospective data exist to support the choice of one type of resistance testing over another, genotypic testing is generally preferred in this situation because of lower cost, more rapid turnaround time, the assay's ability to detect mixtures of wild-type and resistant virus, and the relative ease of interpreting test results **(AIII)**. If therapy is deferred, repeat testing soon before initiation of ART should be considered because the patient may have acquired drug-resistant virus (i.e., superinfection) **(CIII)**.

Standard genotypic drug-resistance testing in ARV-naive persons involves testing for mutations in the RT and PR genes. Although transmission of integrase strand transfer inhibitor (INSTI)-resistant virus has rarely been reported, as use of INSTIs increases, the potential for transmission of INSTI-resistant virus may also increase. Therefore, when INSTI resistance is suspected, providers may wish to supplement standard baseline genotypic resistance testing with genotypic testing for resistance to this class of drugs **(CIII)**.

Use of Resistance Assays in the Event of Virologic Failure

Resistance assays are useful in guiding treatment decisions for patients who experience virologic failure while on ART. Several prospective studies assessed the utility of resistance testing to guide ARV drug selection in patients with virologic failure. These studies involved genotypic assays, phenotypic assays, or both.[6, 39-45] In general, these studies found that changes in therapy that were informed by resistance testing results produced better early virologic response to salvage regimens than regimen changes guided only by clinical judgment.

In addition, one observational cohort study found that performance of genotypic drug-resistance testing in ART-experienced patients with detectable plasma HIV RNA was independently associated with improved survival.[46] Thus, resistance testing is recommended as a tool in selecting active drugs when changing ARV regimens because of virologic failure in persons with HIV RNA >1,000 copies/mL **(AI)** (see Virologic and Immunologic Failure). In persons with HIV RNA >500 copies/mL but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**. Drug-resistance testing in persons with a plasma viral load <500 copies/mL is not usually recommended because resistance assays cannot be consistently performed given low HIV RNA levels **(AIII)**.

Resistance testing also can help guide treatment decisions for patients with suboptimal viral load reduction **(AII)**. Virologic failure in the setting of combination ART is, for certain patients, associated with resistance to only one component of the regimen.[47-49] In this situation, substituting individual drugs in a failing regimen may be a possible option, but this concept will require clinical validation (see Virologic and Immunologic Failure).

In patients who are on a failing first or second ARV drug regimen and experiencing virologic failure or suboptimal viral load reduction, genotypic testing is generally preferred for resistance testing **(AII)**. This is based on the fact that, when compared with phenotypic testing, genotypic testing costs less to perform, has a faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus. In addition, observations show that the assays are comparable predictors of virologic response to subsequent ART regimens.[50]

Addition of phenotypic to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns, particularly to PIs **(BIII)**.

In patients failing INSTI-based regimens, testing for INSTI resistance should be performed to determine whether to include drugs from this class in subsequent regimens **(AII)**; genotypic testing is preferred for this purpose.

When the use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)**. Phenotypic co-receptor tropism assays have been used in clinical practice. A genotypic assay to predict co-receptor use is now commercially available and is less expensive than phenotypic assays. Evaluation of genotypic assays is ongoing, but current data suggest that such testing should be considered as an alternative assay. The same principles regarding testing for co-receptor use also apply to testing when patients exhibit virologic failure on a CCR5 antagonist.[51] Resistance to CCR5 antagonists in the absence of detectable CXCR4-using virus has been reported, but such resistance is uncommon (see Co-receptor Tropism Assays).

Use of Resistance Assays in Pregnant Women

In pregnant women, the goal of ART is to maximally reduce plasma HIV RNA to provide optimal maternal therapy and to prevent perinatal transmission of HIV. Genotypic resistance testing is recommended for all pregnant women before initiation of therapy **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**. Phenotypic testing in those found to have complex drug-resistance mutation patterns, particularly to PIs, may provide additional information **(BIII)**. Optimal prevention of perinatal transmission may require initiation of ART pending resistance testing results. Once the results are available, the ARV regimen can be changed as needed.

Table 4. Recommendations for Using Drug-Resistance Assays (page 1 of 2)

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
In acute HIV infection: Drug-resistance testing is recommended regardless of whether antiretroviral therapy (ART) is initiated immediately or deferred **(AII)**. A genotypic assay is generally preferred **(AIII)**.	If ART is initiated immediately, drug-resistance testing can determine whether drug-resistant virus was transmitted. Test results will help in the design of initial regimens or to modify or change regimens if results are obtained after treatment initiation. Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
If ART is deferred, repeat resistance testing should be considered at the time therapy is initiated **(CIII)**. A genotypic assay generally is preferred **(AIII)**.	If ART is deferred, testing should still be performed because of the greater likelihood that transmitted resistance-associated mutations will be detected earlier in the course of HIV infection. Results of resistance testing may be important when treatment is initiated. Repeat testing at the time ART is initiated should be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection).
In ART-naive patients with chronic HIV infection: Drug-resistance testing is recommended at entry into HIV care, regardless of whether therapy is initiated immediately or deferred **(AII)**. A genotypic assay is generally preferred **(AIII)**.	Transmitted HIV with baseline resistance to at least 1 drug is seen in 6% to 16% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations. Some drug-resistance mutations can remain detectable for years in untreated, chronically infected patients.
If therapy is deferred, repeat resistance testing should be considered before initiation of ART **(CIII)**. A genotypic assay is generally preferred **(AIII)**.	Repeat testing before initiation of ART should be considered because the patient may have acquired a drug-resistant virus (i.e., a superinfection). Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
If an INSTI is considered for an ART-naive patient and transmitted INSTI resistance is a concern, providers may supplement standard resistance testing with a specific INSTI genotypic resistance assay **(CIII)**.	Standard genotypic drug-resistance assays test only for mutations in the RT and PR genes.
If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)** (see Co-receptor Tropism Assays)	(see Co-receptor Tropism Assays)
In patients with virologic failure: Drug-resistance testing is recommended in patients on combination ART with HIV RNA levels >1,000 copies/mL **(AI)**. In patients with HIV RNA levels >500 copies/mL but <1,000 copies/mL, testing may not be successful but should still be considered **(BII)**.	Testing can help determine the role of resistance in drug failure and maximize the clinician's ability to select active drugs for the new regimen. Drug-resistance testing should be performed while the patient is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy.
A standard genotypic resistance assay is generally preferred for patients experiencing virologic failure on their first or second regimens **(AII)**.	Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant HIV.
In patients failing INSTI-based regimens, genotypic testing for INSTI resistance should be performed to determine whether to include drugs from this class in subsequent regimens **(AII)**.	Standard genotypic drug-resistance assays test only for mutations in the RT and PR genes.
If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)** (see Co-receptor Tropism Assays).	
Addition of phenotypic assay to genotypic assay is generally preferred in patients with known or suspected complex drug-resistance patterns, particularly to protease inhibitors (PIs) **(BIII)**.	Phenotypic testing can provide additional useful information in patients with complex drug-resistance mutation patterns, particularly to PIs.

Table 4. Recommendations for Using Drug-Resistance Assays (page 2 of 2)

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
In patients with suboptimal suppression of viral load: Drug-resistance testing is recommended in patients with suboptimal suppression of viral load after initiation of ART **(AII)**.	Testing can help determine the role of resistance and thus assist the clinician in identifying the number of active drugs available for a new regimen.
In HIV-infected pregnant women: Genotypic resistance testing is recommended for all pregnant women before initiation of ART **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**.	The goal of ART in HIV-infected pregnant women is to achieve maximal viral suppression for treatment of maternal HIV infection and for prevention of perinatal transmission of HIV. Genotypic resistance testing will assist the clinician in selecting the optimal regimen for the patient.
Drug-resistance assay not usually recommended	
After therapy is discontinued: Drug-resistance testing is not usually recommended more than 4 weeks after discontinuation of ARV drugs **(BIII)**.	Drug-resistance mutations may become minor species in the absence of selective drug pressure, and available assays may not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value; however, the absence of resistance does not rule out the presence of minor drug-resistant species.
In patients with low HIV RNA levels: Drug-resistance testing is not usually recommended in patients with a plasma viral load <500 copies/mL **(AIII)**.	Resistance assays cannot be consistently performed given low HIV RNA levels.

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Co-Receptor Tropism Assays (Last updated February 12, 2013; last reviewed February 12, 2013)

Panel's Recommendations
• A co-receptor tropism assay should be performed whenever the use of a CCR5 co-receptor antagonist is being considered **(AI)**.
• Co-receptor tropism testing is also recommended for patients who exhibit virologic failure on a CCR5 antagonist **(BIII)**.
• A phenotypic tropism assay is preferred to determine HIV-1 co-receptor usage **(AI)**.
• A genotypic tropism assay should be considered as an alternative test to predict HIV-1 co-receptor usage **(BII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

HIV enters cells by a complex process that involves sequential attachment to the CD4 receptor followed by binding to either the CCR5 or CXCR4 molecules and fusion of the viral and cellular membranes.[1] CCR5 co-receptor antagonists prevent HIV entry into target cells by binding to the CCR5 receptors.[2] Phenotypic and, to a lesser degree, genotypic assays have been developed that can determine or predict the co-receptor tropism (i.e., CCR5, CXCR4, or both) of the patient's dominant virus population. An older generation assay (*Trofile*, Monogram Biosciences, Inc., South San Francisco, CA) was used to screen patients who were participating in clinical trials that led to the approval of maraviroc (MVC), the only CCR5 antagonist currently available. The assay has been improved and is now available with enhanced sensitivity. In addition, a genotypic assay to predict co-receptor usage is now commercially available.

During acute/recent infection, the vast majority of patients harbor a CCR5-utilizing virus (R5 virus), which suggests that the R5 variant is preferentially transmitted. Viruses in many untreated patients eventually exhibit a shift in co-receptor tropism from CCR5 usage to either CXCR4 or both CCR5 and CXCR4 tropism (i.e., dual- or mixed-tropic; D/M-tropic). This shift is temporally associated with a more rapid decline in CD4 T-cell counts,[3, 4] but whether this tropism shift is a cause or a consequence of progressive immunodeficiency remains undetermined.[1] Antiretroviral (ARV)-treated patients with extensive drug resistance are more likely to harbor X4- or D/M-tropic variants than untreated patients with comparable CD4 counts.[5] The prevalence of X4- or D/M-tropic variants increases to more than 50% in treated patients who have CD4 counts <100 cells/mm^3.[5, 6]

Phenotypic Assays

Phenotypic assays characterize the co-receptor usage of plasma-derived virus. These assays involve the generation of laboratory viruses that express patient-derived envelope proteins (i.e., gp120 and gp41). These pseudoviruses, which are replication-defective, are used to infect target cell lines that express either CCR5 or CXCR4.[7, 8] Using the *Trofile* assay, the co-receptor tropism of the patient-derived virus is confirmed by testing the susceptibility of the virus to specific CCR5 or CXCR4 inhibitors *in vitro*. This assay takes about 2 weeks to perform and requires a plasma HIV RNA level ≥1,000 copies/mL.

The performance characteristics of these assays have evolved. Most, if not all, patients enrolled in pre-marketing clinical trials of MVC and other CCR5 antagonists were screened with an earlier, less sensitive version of the *Trofile* assay.[8] This earlier assay failed to routinely detect low levels of CXCR4-utilizing variants. As a consequence, some patients enrolled in these clinical trials harbored low levels of CXCR4-utilizing virus at baseline that were below the assay limit of detection and exhibited rapid virologic failure after initiation of a CCR5 antagonist.[9] The assay has been revised and is now able to detect lower levels of CXCR4-utlizing viruses. *In vitro*, the assay can detect CXCR4-utilizing clones with 100% sensitivity when those clones represent 0.3% or more of the virus population.[10] Although this more sensitive assay has had

limited use in prospective clinical trials, it is now the only one that is commercially available. For unclear reasons, a minority of samples cannot be successfully phenotyped with either generation of the *Trofile* assay.

In patients with plasma HIV-1 RNA below the limit of detection, co-receptor usage can be determined from proviral DNA obtained from peripheral blood mononuclear cells; however, the clinical utility of this assay remains to be determined.[11]

Genotypic Assays

Genotypic determination of HIV-1 co-receptor usage is based on sequencing of the V3-coding region of HIV-1 *env*, the principal determinant of co-receptor usage. A variety of algorithms and bioinformatics programs can be used to predict co-receptor usage from the V3 sequence. When compared to the phenotypic assay, genotypic methods show high specificity (~90%) but only modest sensitivity (~50%–70%) for the presence of a CXCR4-utilizing virus. Given these performance characteristics, these assays may not be sufficiently robust to completely rule out the presence of an X4 or D/M variant.[12]

Studies in which V3 genotyping was performed on samples from patients screened for clinical trials of MVC suggest that genotyping performed as well as phenotyping in predicting the response to MVC.[13-15] On the basis of these data, accessibility, and cost, European guidelines currently favor genotypic testing to determine co-receptor usage.[16] An important caveat to these results is that the majority of patients who received MVC were first shown to have R5 virus by a phenotypic assay (*Trofile*). Consequently, the opportunity to assess treatment response to MVC in patients whose virus was considered R5 by genotype but D/M or X4 by phenotype was limited to a relatively small number of patients.

Use of Assays to Determine Co-Receptor Usage in Clinical Practice

An assay for HIV-1 co-receptor usage should be performed whenever the use of a CCR5 antagonist is being considered **(AI)**. In addition, because virologic failure may occur due to a shift from CCR5-using to CXCR4-using virus, testing for co-receptor usage is recommended in patients who exhibit virologic failure on a CCR5 antagonist **(BIII)**. Virologic failure also may be caused by resistance of a CCR5-using virus to a CCR5 antagonist, but such resistance is uncommon. Compared to genotypic testing, phenotypic testing has more evidence supporting its usefulness. Therefore, a phenotypic test for co-receptor usage is generally preferred **(AI)**. However, because phenotypic testing is more expensive and requires more time to perform, a genotypic test to predict HIV-1 co-receptor usage should be considered as an alternative test **(BII)**.

A tropism assay may potentially be used in clinical practice for prognostic purposes or to assess tropism before starting ART if future use of a CCR5 antagonist is anticipated (e.g., a regimen change for toxicity). Currently, sufficient data do not exist to support these uses.

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HLA-B*5701 Screening (Last updated December 1, 2007; last reviewed January 10, 2011)

Panel's Recommendations
• The Panel recommends screening for HLA-B*5701 before starting patients on an abacavir (ABC)-containing regimen to reduce the risk of hypersensitivity reaction (HSR) **(AI)**. • HLA-B*5701-positive patients should not be prescribed ABC **(AI)**. • The positive status should be recorded as an ABC allergy in the patient's medical record **(AII)**. • When HLA-B*5701 screening is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of HSR **(CIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

The ABC HSR is a multiorgan clinical syndrome typically seen within the initial 6 weeks of ABC treatment. This reaction has been reported in 5%–8% of patients participating in clinical trials when using clinical criteria for the diagnosis, and it is the major reason for early discontinuation of ABC. Discontinuing ABC usually promptly reverses HSR, whereas subsequent rechallenge can cause a rapid, severe, and even life-threatening recurrence.[1]

Studies that evaluated demographic risk factors for ABC HSR have shown racial background as a risk factor, with white patients generally having a higher risk (5%–8%) than black patients (2%–3%). Several groups reported a highly significant association between ABC HSR and the presence of the major histocompatibility complex (MHC) class I allele HLA-B*5701.[2-3] Because the clinical criteria used for ABC HSR are overly sensitive and may lead to false-positive ABC HSR diagnoses, an ABC skin patch test (SPT) was developed as a research tool to immunologically confirm ABC HSR.[4] A positive ABC SPT is an ABC-specific delayed HSR that results in redness and swelling at the skin site of application. All ABC SPT–positive patients studied were also positive for the HLA-B*5701 allele.[5] The ABC SPT could be falsely negative for some patients with ABC HSR and, at this point, is not recommended for use as a clinical tool. The PREDICT-1 study randomized patients before starting ABC either to be prospectively screened for HLA-B*5701 (with HLA-B*5701–positive patients not offered ABC) or to standard of care at the time of the study (i.e., no HLA screening, with all patients receiving ABC).[6] The overall HLA-B*5701 prevalence in this predominately white population was 5.6%. In this cohort, screening for HLA-B*5701 eliminated immunologic ABC HSR (defined as ABC SPT positive) compared with standard of care (0% vs. 2.7%), yielding a 100% negative predictive value with respect to SPT and significantly decreasing the rate of clinically suspected ABC HSR (3.4% vs. 7.8%). The SHAPE study corroborated the low rate of immunologically validated ABC HSR in black patients and confirmed the utility of HLA-B*5701 screening for the risk of ABC HSR (100% sensitivity in black and white populations).[7]

On the basis of the results of these studies, the Panel recommends screening for HLA-B*5701 before starting patients on an ABC-containing regimen **(AI)**. HLA-B*5701–positive patients should not be prescribed ABC **(AI)**, and the positive status should be recorded as an ABC allergy in the patient's medical record **(AII)**. HLA-B*5701 testing is needed only once in a patient's lifetime; thus, efforts to carefully record and maintain the test result and to educate the patient about its implications are important. The specificity of the HLA-B*5701 test in predicting ABC HSR is lower than the sensitivity (i.e., 33%–50% of HLA-B*5701–positive patients would likely not develop confirmed ABC HSR if exposed to ABC). HLA-B*5701 should not be used as a substitute for clinical judgment or pharmacovigilance, because a negative HLA-B*5701 result does not absolutely rule out the possibility of some form of ABC HSR. When HLA-B*5701 screening is not

readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of ABC HSR **(CIII)**.

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